to meaningfully enhance the treatment of depression.

There may be a consensus that a serotonin reuptake inhibiting antidepressant is the first treatment to try in most individuals with the diagnosis of major depressive disorder, but we know that fewer than half of patients benefit sufficiently, that many experience side effects that are not matched by benefits, and that there is little evidence on what treatments should be attempted next. Many have lamented how it is possible that we still do not have personalized treatment given the amount of work that has been done. The number of articles published on this topic may be misleading. The reason why second and third line treatment for depression is still artisanal is that there is far too little data to personalize treatment choice.

The largest study of depression treatment completed to date – the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study – has failed to personalize the second and third line treatment choices for depression because it was too small. By the time STAR*D participants progressed to the third step, the numbers of patients allocated to specific treatments were too low to allow meaningful analysis of predictors. Genetic data were available for only half STAR*D participants, further compromising the power to find biomarkers that could facilitate the choice between second and third line treatments. Genetic case-control association studies of schizophrenia, depression and other disorders have taught us that sample sizes of many thousands are needed to leverage genomic information and enable meaningful predictions. For treatment predictions, these sample sizes have to be multiplied by the number of alternative treatments that need to be tested.

With today's technology, it is possible to create, combine and exploit datasets of hundreds of thousands for common disorders like depression. The way to do it may need to work with human motivation so that the process and not just the outcomes are meaningful for patients and for clinicians. The first step will be to motivate the collection of diagnostic information and regular outcome ratings in routine clinical practice. Person-centered care with active engagement of patients in clinical decisions offers a framework for achieving such routine information collection⁷.

People living with depression come with their values and preferences and want to be actively involved in discussions about their care. Patients will complete regular outcome measures if they know that these meaningfully contribute to their care. Investigators of the Canadian Depression Research and Intervention Network have piloted a person-centered measurement-based care model where patients are given the option to complete regular measures on Internet-enabled devices and request feedback that serves to enhance their participation in collaborative decision making with their clinicians. Clinicians are able to access the information and also contribute diagnosis and rating scales. Based on the information provided by clinicians and patients, a feedback is generated that selects relevant recommendations from current best practice guidelines. In this model, patients are motivated to contribute data that serve both clinical and research purposes because they see the impact of the information on their care. They in turn motivate their clinicians to participate in the information gathering and feedback process. Patients are also asked for consent to use their data for clinical research and

link their data with health care databases. The platform is improving outcomes of depression in real time, allows efficient evaluation of services, and at the same time contributes to the accrual of data that will eventually help personalize treatment for depression.

In a large database, it will be possible to look up individuals who resemble a given patient on a number of factors and recommend treatments that worked for that patient. Where two or more treatments are at equipoise, they can be compared using the efficient randomized registry design embedded in routine health care⁸. The results of such large pragmatic comparisons will gradually allow exploring further steps in treatment selection or testing novel treatments.

The vision outlined above has only been partially piloted. The early experience leads us to believe that the treatment for depression has to be person-centered and measurement-based before it can be meaningfully personalized.

Rudolf Uher

Dalhousie University Department of Psychiatry, Halifax, NS, Canada

The author is supported by the Canada Research Chairs Program.

1. Uher R, Perlis RH, Henigsberg N et al. *Psychol Med* 2012;42:967-80.
2. Uher R, Tansey KE, Dew T et al. *Am J Psychiatry* 2014;171:1278-86.
3. Guo T, Xiang Y-T, Xiao L et al. *Am J Psychiatry* 2015;172:1004-13.
4. Peters EJ, Slager SL, Kraft JB et al. *PLoS One* 2008;3:e1872.
5. GENDEP investigators, MARS investigators, STAR*D investigators. *Am J Psychiatry* 2013; 170:207-17.
6. Perlis RH. *World Psychiatry* 2016;15:228-35.
7. Dixon LB, Holoshitz Y, Nossel I. *World Psychiatry* 2016;15:13-20.
8. Lauer MS, D'Agostino RB Sr. *N Engl J Med* 2013;369:1579-81.

DOI:10.1002/wps.20363

Carving depression at its joints?

Personalization of treatments has long been an aspiration for medicine and has recently evolved into a sophisticated practice for the treatment of some diseases. Although in psychiatry treatment deci-

sions are usually based on the individual patient and his/her needs, there is a lack of information about how the benefits and harms of individual pharmacological agents (and indeed treatments in other

modalities) differ from patient to patient and very limited data on which to base the choice between treatment options for individual patients. The thoughtful paper by R. Perlis¹ addresses the challenges in

personalization of antidepressant treatment and highlights various important scientific questions thereof.

Perlis suggests that available phenomenological patient-level features may be of more help than generally acknowledged for establishing probability of response. Whilst many might have sympathy with this view, history is replete with debates about the therapeutic utility of various subdivisions of depression, perhaps most notably the prolonged dispute between the Newcastle categorical² and the Maudsley dimensional³ approach. Such arguments remain inconclusive.

However, other recent work has focused on the cases of depression which have undiagnosed bipolar disorder and highlighted this as an area potentially important for personalizing treatment. The seminal paper by Angst et al⁴ showed that broad diagnostic criteria (in comparison with DSM-IV-TR criteria) identified a large number of additional patients with major depressive episodes who were likely manifesting depression as part of a bipolar disorder. These authors suggest that additionally considering family history, illness course and clinical status, as well as diagnostic criteria, may provide useful information for physicians when assessing evidence of bipolarity in patients with major depressive episodes. Many such patients (with major depressive episodes as part of a bipolar disorder) will be treated with but not respond to antidepressants. This has led to the notion being promulgated that all antidepressants should be, as a regulatory requirement, tested in bipolar major depressive episodes as well as in unipolar depression⁵.

Perlis also reviews biological approaches, but the question remains: are the currently available putative biomarkers of antidepressant response really more robust and consistent tools compared to “artisanal” practice? For example, the correlation between plasma drug levels and clinical response is weak and not only are drug plasma levels poorly associated with doses of drugs, but there is also a significant dissociation between brain and plasma kinetics, as demonstrated by positron emission tomography (PET) receptor

occupancy studies⁶. Many factors, other than plasma levels, moderate drug action in the central nervous system. These factors will affect the predictive ability of pharmacogenomic biomarkers that are directly linked to pharmacokinetic variables, for example those which are genetic determinants of drug metabolism, and limit their potential contribution in increasing precision of pharmacotherapies.

The development of high precision pharmacotherapies is typically driven by the combination of three factors: a) treatments are potentially highly efficacious if the right treatment is given to the right person; b) treatments are very expensive; c) treatments may be associated with serious adverse effects. The need for careful pre-selection of a specific treatment for the right patients becomes highest in those diseases in which it is most important to direct expensive investments to the patients identified with highest-benefit and lowest-risk potential. For mood disorders as a whole, there is arguably less of a compelling need for this kind of “precision” treatments: pharmacotherapies for depression are relatively affordable, compared to those for autoimmune or neoplastic diseases, and very serious adverse effects are rare. Thus, clinicians may end up trusting more their own “artisanal” judgment based on experience than not very informative evidence-based medicine inspired treatment protocols and guidelines.

The integration of multimodal biomarker approaches may potentially increase precision, but at the moment their cost and complexity is high and the utility of this approach unproven. New biomarker approaches (transcriptomic, proteomic, genomic and telomeric) may potentially change this⁷. However, it will be important to establish how much higher remission rates can be achieved with such multimodal biomarkers informing personalized treatment before advocating this approach. Even if this could not be translated into clinical practice because of cost and complexity, proof-of-concept studies would answer crucial clinical research questions that

have remained unresolved despite the overall progress in neuroscience.

Where does all of this leave us? It may be worthwhile pausing to reflect on how progress was achieved recently in other fields of medicine. Although we often feel that our problems are unique to psychiatry, the confounding effects of heterogeneity are not confined to mood disorders and have been addressed in other fields of study by focussing on the most reliable diagnoses which are most tractable for research⁸. This has produced major advances in the understanding of Alzheimer’s disease, which have underpinned ongoing therapeutic research. This approach has also been shown to be practical in familial studies of lithium response⁹. Extending this approach further to mood disorders might mean focusing, for instance, on bipolar I disorder with a strong familial component. We could apply this “narrow” approach to therapeutic research in this area and combine it with the multimodal biomarker notions outlined above. Any relationship between biomarkers and therapeutic responses could then be further verified in larger clinical populations.

What of “broad” approaches, i.e. studying a multiplicity of factors in large groups of heterogeneous patients? This will undoubtedly continue and may be made potentially more fruitful by recent developments. The recent revision of DSM introduced new ways of splicing major depression, including the delineation of various facets of the clinical symptomatology. An interesting example of the potential advantages of this development is a recent study on major depression with mixed features¹⁰.

Future progress will likely come from the application of both “narrow” and “broad” approaches, focused on valid and well-characterized patient samples, trying, to quote Socrates, to “divide things again by classes, where the natural joints are”.

Allan H. Young, Alessandro Colasanti

Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neurosciences, King’s College London, London, UK

1. Perlis RH. *World Psychiatry* 2016;15:228-35.

2. Roth M. *Acta Psychiatr Scand* 1981;63(Suppl. 290):42-51.
3. Kendell RE. *Scott Med J* 1978;23:61-3.
4. Angst J, Azorin JM, Bowden CL et al. *Arch Gen Psychiatry* 2011;68:791-8.
5. Young AH. *Aust N Z J Psychiatry* 2012;46:293-4.
6. Suhara T. *Arch Gen Psychiatry* 2003;60:386-91.
7. Gururajan A, Clarke G, Dinan TG et al. *Neurosci Biobehav Rev* 2016;64:101-33.
8. Guerreiro R, Hardy J. *Neurotherapeutics* 2014; 11:732-7.
9. Grof P, Duffy A, Alda M et al. *Acta Psychiatr Scand* 2009;120:378-85.
10. Suppes T, Silva R, Cucchiaro J et al. *Am J Psychiatry* 2016;173:400-7.
DOI:10.1002/wps.20367

Pragmatic treatment options for depression and anxiety disorders are needed

Major depressive disorder (MDD) is a common disorder with a lifetime risk around 35%¹. It is a significant cause of mortality and the second leading cause of years lived with disability worldwide². At many levels, the similarities between MDD and the anxiety disorders are much stronger than the differences. For instance, these disorders share genetic, temperamental and environmental risk factors, frequently co-occur, and cognitive behavior therapy (CBT) and antidepressant drugs are recommended as principal treatments for both³. It will therefore be very difficult to locate pathologies and treatments that are specific to subtypes of depression without considering their relationship with anxiety. As a result, we broaden our comment on Perlis' proposal⁴ to reduce personalized (or non-evidence based) medicine in favor of precise (evidence-based) medicine to include both depression and anxiety.

Despite the availability of evidence-based treatments and the energetic "Reduce Mental Illness" campaigns that have been carried out in many countries, the years lived with disability due to these disorders have not declined over the past two decades². This burden persists, at least in part, because only 39% of adults who met criteria for a depressive and/or anxiety disorder in the past year sought help for their mental health problems⁵. Additionally, the burden associated with depression and anxiety continues, as Perlis suggests, because of the type and dose of treatment that patients receive from their mental health professionals.

Evidence-based guidelines for the treatment of depression and anxiety recom-

mend a stepped approach to care where patients are prescribed treatments in order of their intensity, effect and cost⁶. Specifically, CBT is the recommended first-line psychological treatment for mild to moderate depression and the anxiety disorders, and in combination with pharmacotherapies for severe and complex cases^{7,8}. Although these guidelines were developed to translate advances in medical research into clinical practice, their dissemination does not necessarily improve clinical outcomes. Indeed, of those people who met criteria for depression and/or an anxiety disorder in the past year and sought help for their mental health problems, 67% were offered an evidence-based treatment and only 41% received a minimally adequate dose of treatment⁵.

Even when people receive a minimally adequate dose of treatment, a significant proportion continue to experience distress and impairment. This is because the recommended psychological and pharmacological interventions range in number needed to treat (NNT) from ~2 to 16, depending on the comparator⁹. Perlis argues that the NNT of antidepressants could be improved if: a) specific drugs were linked to specific disorder subtypes; b) diagnostic tools sensitive to these mechanisms of action were disseminated; and c) clinicians implemented these tools in practice. To this end, he states that "numerous investigations of predictors... of treatment response have been reported over the past five decades"⁴. Yet, to our knowledge, none of these predictors have been associated with Level 1 evidence that a certain treatment for MDD is superior for people who have certain characteristics. Level 1 evi-

dence would require both independently replicated superiority (RCTs) with representative groups of patients in which the treatment is shown to remedy the core pathology in the target group *and* that there are no methodologically sound rebuttals.

We thank Perlis for mentioning a five-decade time frame. Five decades ago, we, in a study to identify core pathologies, divided a cohort of inpatients with a primary diagnosis of depression into those with "endogenous" or "neurotic" depression on the basis of clinical presentation, family history and longitudinal data. At intake, discrimination between endogenous and neurotic depression was strong, but the data were equally compatible with Grinker et al's five-division classification¹⁰, which weakened the findings. At the 15-year follow-up, the overall outcomes of people identified with endogenous or neurotic depression were equally poor, with two relatively minor differences: endogenous depression showed more frequent but shorter hospital admissions, and the outcome in neurotic depression was more strongly related to the level of neuroticism at the index admission¹¹.

Identifying disorder subtypes for targeted treatment, as Perlis says, is likely to be time consuming and difficult. Indeed, seven types of first line drug therapies for MDD – selective serotonin reuptake inhibitors (SSRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NARIs), melatonin agonists, serotonin modulators – that notionally target different pathologies are